23. (Amended) A pharmaceutical composition comprising the antibody of claim 1 and a pharmaceutically acceptable carrier or diluent.

29. (Amended) A pharmaceutical composition comprising the antibody of claim 13 and a pharmaceutically acceptable carrier or diluent.

REMARKS

As initial matters, Applicants note that a Revocation of Prior Powers of Attorney and appointment of new powers was submitted to the PTO on October 29, 2001. The documents authorized the undersigned to prosecute this case on behalf of Applicants. Acknowledgement of the documents is respectfully requested. A copy of the documents is provided as a convenience to the Examiner.

Further, Applicants request that the attorney docket no. in this case be changed from "04995.0032-0" to -- 56273/ (71758) --. The Examiner is thanked in advance for attention to this detail.

Turning to the present Action, claims 23 and 29 were rejected under 35 USC §112, second paragraph, as being indefinite. Although Applicants respectfully disagree with the position taken, grounds for it have been addressed by this submission.

Claims 1, 13-20, 23 and 29 stand rejected under 35 USC §112, first paragraph, as non-enabling. The rejection as to claims 23 and 29 has already been addressed. Applicants respectfully disagree with remaining basis for the rejection.

As an initial matter, Applicants gratefully acknowledge that the Examiner has found the specification enabling for a humanized monoclonal antibody which binds to Shiga toxin 1. Action at pg. 3, paragraph 3.

As understood, the position was taken that Applicants' specification does not show how to make and use humanized monoclonal antibodies which bind to Shiga toxin type 1 variants or for those antibodies that bind "at least part of" the variable region from SEQ ID NO:42 and SEQ ID NO:43. Applicants disagree as follows.

As the specification makes clear, practice of the invention is not limited to a particular humanized monoclonal antibody or to a specific Shiga toxin.

With respect to the Shiga toxin, Applicants' disclosure teaches a variety of such toxins, collectively referred to as "Stx", that encompass a family of bacterial proteins produced by EHEC and *Shigella dysenteriae*. See eg., pg. 2, last full paragraph (disclosing a variety of Shiga toxins); pgs. 2-3, bridging paragraph and first full paragraph on pg. 3, (describing additional Shiga toxins and variants thereof). The specification also discloses immunological relatedness ("cross-reactivity") between the Shiga toxins eg., at pgs. 3-4, bridging paragraph. Additional illustrations of acceptable Stx are disclosed throughout the present application. See pgs. 2-4 of the application and references cited therein.

In particular, methods of preparing and using Stx-1 and Stx-2 toxin are described by Applicants eg., at pgs. 27-32 (Examples 7-8).

Turning to the humanized monoclonal antibodies, Applicants' disclosure provides for several of them.

For example, see pgs. 11-18 (Examples 1-3) describing production of the H13C4 antibody. See also Examples 4-7 on pgs. 19-28 disclosing how to make the H11E10 antibody. Antibodies having particular nucleic acid and amino acid structures are shown in Figures 3 and 6, for instance. Moreover, disclosure relating to preferred complimentarity determining regions

(CDRs) and methods for manipulating same to achieve humanization is provided throughout the application including Figure 3 and the examples section. Antibodies that have the same binding activity as at least two well characterized murine monoclonal antibodies are also disclosed. Preferred antibodies include those which have modifications that do not appreciably diminish binding. See pg. 9. Pages 7-8 under "Detailed Description of the Invention" provide for additional humanized monoclonal antibodies that bind such Shiga toxin proteins.

The Office has acknowledged that monoclonal antibodies are generally "readily produced". Action at pg. 5. Applicants agree and further point out that such antibodies can be readily modified to include deletions, additions, and substitutions that do not appreciably diminish Stx binding. See pg. 9 of the specification, for instance.

Accepted methods for detecting and quantifying Stx binding are taught eg., in the Examples section.

For example, Applicants' disclosure teaches immunological assays for identifying and testing suitable antibodies *in vitro*. See Example 7 (disclosing preferred Vero cell and antisera neutralization assays). A passive immunization protocol for testing such antibodies *in vivo* has also been disclosed eg., in Example 8, pgs. 29-32.

In sum, a worker in the field would understand that the instant disclosure provides for a variety of humanized monoclonal antibodies and binding shiga toxin antigens. One of skill would also appreciate that the *in vitro* and *in vivo* assays of the invention provide a useful paradigm for identifying and testing humanized monoclonal antibodies including suitable fragments or derivatives thereof.

As understood, the rejection takes the position that notwithstanding Applicants' disclosure of suitable humanized monoclonal antibodies and Stx antigens, use of anything but a humanized monoclonal antibody that binds Shiga toxin 1 is not enabled by the specification on grounds that it would require undue experimentation to make and use. Office Action at pg. 4. Applicants respectfully disagree.

As discussed, the specification provides examples of suitable humanized monoclonal antibodies for use with the claimed invention including, but not limited to, the specific antibody/antigen referenced by the PTO at pg 4 of the Action.

For example, if another particular antibody other than that cited by the Office is desired eg., one that includes a modification or at least a portion of the variable sequence provided in SEQ ID Nos. 42 and 43, the specification provides ample guidance about selecting such an antibody. As an illustration, it is well-known in the field that particular antibody fragments such as Fab and Fv routinely bind antigen. These and other suitable fragments and derivatives could be tested in accord with the assays disclosed in Applicants' specification to select those molecules thereof that bind Stx antigen.

For example, preferred humanized monoclonal antibodies H11E10 and H13C4 are reported to exhibit favorable Stx binding using Stx-1 and Stx-2 peptide antigens. See Example 7 at pgs. 27-28, for instance.

As stated, the chemical structure of a humanized monoclonal antibody has been disclosed both at the amino acid and nucleic acid levels. See Figures 3 and 6, for example. Important function domains in the structure, specifically CDRs have been recognized and identified. See Figure 6. Methods for producing suitable humanized monoclonal antibody, preferably by use of conventional recombinant means have been disclosed. See the Examples section.

Accordingly, it is believed that any testing needed to identify and/or confirm the humanized monoclonal antibodies of the claims is well within the level of experimentation permitted by the Federal Circuit. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Applicants note that *Wands* especially held that routine testing to select monoclonal antibodies is permissible.

Applicants disagree with the rejection on other grounds.

For example, a worker in this field would be able to use the guidance provided by the instant disclosure to select appropriate humanized monoclonal antibodies including those having at least part of the variable region of SEQ ID NOs. 42-43. Any inoperable embodiments of the type described by the rejection could be readily avoided. As described by the Court of Customs and Appeals:

> [M]any patented claims read on vast numbers of inoperative embodiments in the trivial sense that they can and do omit 'factors which must be presumed to be within the level of ordinary skill in the art.' ... There is nothing wrong with this so long as it would be obvious to one of skill in the art how to include these factors in such manner as to make the embodiment operative rather than inoperative. *In re Cook and Merigold*, 169 USPQ 299, 302 (C.C.P.A. 1971) (quoting *In re Skrivan*, 166 USPQ 85, 88 (C.C.P.A. 1970)).

Thus, one of skill having read Applicants' disclosure would know to identify appropriate humanized monoclonal antibodies including those having at least part of the variable region of SEQ ID Nos. 42-43. Even if one assumes, *arguendo*, that a particular antibody did not exhibit acceptable Stx binding, that result by itself, would not support the present enablement rejection. The worker would understand that another antibody including a portion thereof as provided by the specification, could be tested and identified for suitable activity. The rejection has not provided any reason to doubt that the guidance provided by Applicants' disclosure could not be used to identify a range of acceptable humanized monoclonal antibodies including those in which at least part of the variable region is from SEQ ID Nos. 42 and 43.

It is noted that the rejection seems premised on the position that only claims drawn to an exemplified invention embodiment satisfy the requirements of Section 112, first paragraph, notwithstanding the broader invention Applicants disclose.

Respectfully, such a position conflicts with established patent law. It is well-recognized that a patentee's invention is properly broader than specific embodiments identified in an application. Thus in *In re Anderson*, the CCPA reversed a rejection under Section 112, first paragraph and noted in particular (176 USPQ at 333):

> What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the clear disclosure of a broader invention. **This it may not do**.... There is no doubt that a patentee's invention may be broader than the particular embodiment shown in his specification. A patentee is not only entitled to narrow claims directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities. (emphasis added).

Here, the claimed invention is broader than use of the particular humanized monoclonal antibody singled-out in the rejection. As taught throughout Applicant's disclosure, the invention is compatible with a variety of suitable humanized monoclonals including those in which at least part of the variable region is from SEQ ID Nos. 42-43.

In view of the guidance provided by the specification and applicable patent law, the information related at pgs. 4-5 of the Office Action (alleging need for an extensive structure-function analysis) is simply not required to practice the claimed invention.

Finally, it is noted that the Office has acknowledged the high level of knowledge in the art of making monoclonal antibodies. Office Action at pg. 5. Such knowledge is presumed to include a great deal of information about humanized monoclonals including disclosure relating to fragments and derivatives thereof such as Fab and Fv.

With respect to the Office rejection of claim 2, Applicants do not believe that the Campbell reference, as cited, is relevant.

For example, the reference is nearly 20 years old. Moreover, it pre-dates important advances in the field since 1984. To cite that reference now is to take issues raised by Campbell completely out of context and without redress from the many immunology advancements made since then. Accordingly, the reference is out-of-date, inappropriate, and as such it fails to support the position of the USPTO.

However even if Campbell stands as a reference, it lends no support to the rejection. As cited, Campbell discloses full characterization of antibodies; specifically reproduction of identical cell lines and antibody. Respectfully, such tasks are not needed to make and use the invention claimed. Claim 2 recites a humanized monoclonal antibody having the same binding specificity as the deposited antibodies. That functional binding correspondence need not depend on having structural identity between antibodies as suggested by the Office Action.

In view thereof, reconsideration and withdrawal of the §112, first paragraph, rejection are requested.

Claims 1, 2, 13-20 and 29 stand rejected as being obvious over any one of Speirs et al. (*Can. J. Microbiol.* (1991) 37: 650' "Speirs") or O'Brien et al. (US Pat. No. 5,747,272) in view of Shitara et al. (U.S. 5, 866, 692). Applicants must respectfully traverse.

As an initial matter, Applicants wish to point out an inconsistency in the positions taken by the PTO.

Specifically, it is not seen how the Patent Office can allege that the invention of claims 1, 2, 13-20, 23 and 29 are obvious, yet at the same time, take the position that it would require undue experimentation to make in the absence of a deposit. See pgs. 4-9 of the Action dated December 14, 2000 (discussing an alleged need for a deposit under 35 USC §112). Respectfully, there can be no *prima facie* case for obviousness since the Office has contended, on the record, that Applicants' invention would require undue experimentation to make. That position was taken against Applicant in the face of Speirs, O'Brien, Shitara and other art. To advance both

positions against Applicant, as has been done in this case, is illogical and places an unfair burden on Applicants. On this basis alone, the instant obviousness rejection should be withdrawn.

However even if that ground for obviousness stands, the rejection fails on other grounds.

As understood, the position taken by the PTO is that it would be obvious to synthesize and express a chimeric antibody that binds to Shiga-like toxin type 2 and that it would be obvious to humanize that antibody. The position is believed to arise from Shitara's report of a DNA-based method for humanizing antibodies (see eg., cols. 3-4 of the patent). Embedded in the PTO's argument is the contention that it would be obvious to make DNA encoding Applicants' antibody; specifically to isolate, sequence and analyze that DNA, and to humanize antibody encoding DNA sequence along lines of Shitara as cited. Respectfully, the position is at odds with decisions of the Federal Circuit and current USPTO examination practice.

None of the references as relied on provide any amino acid or nucleic acid sequence information relating to a humanized an anti-shiga toxin monoclonal antibody.

The Federal Circuit has made it abundantly clear that not even a prior art disclosure of a protein sequence renders a particular DNA obvious. See eg., *In re Deuel*, 51 F.3d 1552, 1558-59, (Fed. Cir. 1995). More is needed. However, in the instant case, the PTO has not even reached the threshold addressed by *Duel.* That is, it has not cited any sequence of any humanized anti-shiga toxin monoclonal antibody in formulating the rejection. Nonetheless, the Office urges that obtaining Applicants' antibody would be obvious in the face of no sequence information. Respectfully, the position is completely without merit under the case law and should be withdrawn. Not even a partial protein sequence of any humanized anti-shiga toxin monoclonal antibody has been cited against Applicants. Even assuming, *arguendo*, that such minimal information was cited, the instant obviousness rejection would still fail in view of applicable case law. See *In re Deuel,* Id. MPEP § 2144.09. See also See *In re Bell* 51 F.3d 1552 (Fed. Cir. 1995).

In contrast, it is Applicants who disclosed how to humanize an anti-Stx 1 antibody (13C4), specifically by showing how to identify and clone a 13C4 antibody variable cDNA; how to construct and express vectors encoding appropriate antibody heavy and light chains including suitable subcloning manipulations. See Examples 1-2 on pgs. 11-17. Stable production of a recombinant mouse/chimera 13C4 antibody was also shown on pgs. 18-19.

Importantly, Applicants sequenced the DNA of EHEC anti-Stx2 antibody 11E10 to assist the disclosed antibody humanization process. See the disclosure at pgs. 19-23. That sequence information is provided in Figure 6 and was instrumental in identifying and manipulating certain CDR regions. Also importantly, the DNA sequence obtained by Applicants assisted efforts to make a variety of useful PCR primers. See eg., Figure 5.

None of the cited references, when taken alone or in combination, teaches or suggests how to make or manipulate the DNA information furnished by Applicants. There would be no motivation to make Applicants' humanized monoclonal antibodies in view of those references.

Accordingly, there is no *prima facie* case for obviousness of the claims. Reconsideration and withdrawal of the rejection are requested.

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

Although it is not believed that any additional fee is required to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. **04-1105** should any fee be deemed necessary.

Attached to this submission is a marked-up version of the changes made to the specification and claims. The attached page is captioned "version with markings to show changes made".

Respectfully submitted,

Date: 21 November 2001

Robert L. Buchanan (Reg. No. 40,927)
EDWARDS & ANGELL, LLP
DIKE, BRONSTEIN, ROBERTS
& CUSHMAN
Intellectual Property Practice Group
P. O. Box 9169
Boston, Massachusetts 02209
Tel.: (617) 439-4444
Fax: (617) 439-4170 / 7748

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 3-12, 21, 22, 24-28, 30 and 31 have been cancelled without prejudice.

Claims 23 and 29 have been amended as follows:

23. (Amended) A pharmaceutical composition comprising the antibody of claim 1 ~~, or fragment or derivative thereof,~~ and a pharmaceutically acceptable carrier or diluent.

29. (Amended) A pharmaceutical composition comprising the antibody of claim 13~~, or fragment or derivative thereof,~~ and a pharmaceutically acceptable carrier or diluent.

#182756